MARK P. BIRKENBACH, M.D., KOVLER LABORATORIES, UNIVERSITY OF CHICAGO $35,000

Analysis of Novel B Lymphocyte Cytokine Receptor, EBI 3

Epstein-Barr Virus (EBV) infects B lymphocytes, which are the antibody-producing cells of the human immune system. This frequently results in the acute infectious mononucelosis syndrome, characterized by a marked increase in the number of peripheral blood lymphocytes, representing both EBV-infected B lymphocytes induced to multiply by the virus, and uninfected immune cells responding to the infection. In addition, EBV is frequently found in human malignant tumors of B lymphocytes, including Burkitt lymphoma and tumors which arise in patients who are immunosuppressed as a result of AIDS or immunosuppressive drug therapy following organ transplantation. Normal peripheral blood B lymphocytes infected with EBV in culture are stimulated to grow and will proliferate indefinitely. It is likely that the mechanisms which allow EBV to form tumors are related to its ability to alter the growth of cells it infects. To elucidate the mechanisms by which EBV induces cells to grow, I have identified nine novel cell genes which are turned on by virus infection. One of these genes, EBI 3, has the structural characteristics of the cytokine receptor family of molecules. Typically, members of this family are present on lymphocyte surfaces and function as critical mediators of immune cell function by receiving regulatory signals from outside the cell. In other cases, these receptors may themselves be secreted by cells to act soluble growth-regulating factors on other immune cells. These facts suggest that EBI 3 may play an important role in EBV-mediated transformation by modulating the growth of infected cells, or altering responses of the immune system against infection. The proposed studies will examine the expression of EBI 3 and its function in normal and EBV-infected lymphocytes. The EBI 3 structure suggests that it represents a secreted molecule. In other cytokine receptors, both secreted and cell surface forms of the same gene product have been identified. Initial experiments will determine whether EBI 3 is expressed on cell surfaces, is secreted as a soluble factor, or exists in both forms. Associated molecules will be identified using the EBI 3 antibodies to retrieve EBI 3 protein molecules under conditions where interactions with other molecules can be stably maintained. Future studies will be directed toward identifying these associated molecules and determining the effects of EBI 3 on lymphocyte growth and functional activity. The proposed experiments should increase our understanding of how lymphocyte growth and immune responses are regulated. It is hoped that through this understanding, the processes which allow lymphocytes to escape normal regulatory mechanisms and grow in uncontrolled fashion may be elucidated. Ultimately, identification of hormones which modulate lymphocyte growth may allow development of novel approaches to treatment of abnormal lymphocyte proliferations such as leukemia and lymphoma.